Pharmacia & Upjohn

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Dockets Management Branch HFA - 305
Food and Drug Administration
5600 Fishers Lane, Room 1061
Rockville, MD 20852

Docket No. 98D-1168
Draft Guidance for Industry on ANDA's:
Impurities in Drug Products

Dear Sir/Madam:

Attached are two copies of the Pharmacia & Upjohn Company's comments regarding the Draft Guidance for Industry on ANDA's: Impurities in Drug Products which appeared for comment in the January 5, 1999 Federal Register (Docket No. 98D - 1168). We greatly appreciate the opportunity to provide these comments.

Sincerely,

D. T. Fagan, PhD
Attachments

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98D-1168

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FDA's December 1998 Draft Guidance for Industry – ANDAs: Impurities in Dry Products
Pharmacia and Upjohn Comments

We agree that ANDAs (like NDAs) should include a scientific assessment of degradation pathways, qualification of degradation products, and appropriate limits. We further agree with the draft guidance in referencing the ICH Q3B document, and the accompanying requirements for new drugs. However, there are four aspects of this draft that are objectionable, as summarized below.

1. There is a provision for FDA to provide analytical methods through FOI. Analytical methods and limits used in the process and/or for quality control purposes are developed by the innovator and submitted to the NDA. This information is proprietary as it represents internal technical know how and trade secrets related to the drug and dosage form in question. FDA's NDA regulations state that "Manufacturing methods or processes, including quality control procedures," are not available for public disclosure unless they have been previously disclosed to the public or relate to a product or ingredient that has been abandoned, and they do not represent a trade secret or confidential commercial information.[1] **Therefore, analytical methods and limits, including degradation assay methods, should be held in confidence by the agency when submitted to an IND or NDA and not distributed through FOI.** The rationale for his is more fully explained in the Attachment.

2. We also object to the provision in the draft for degradation product levels to exceed the reference drug by a factor of 2. These limits are qualified based on human and animal studies, and linked to the stability of the product. Doubling the limit that was accepted by the agency at time of NDA approval is not available to the innovator, nor is it allowed by ICH Q3B and therefore should not be available to an ANDA sponsor. **All sponsors (whether for NDAs or ANDAs) should meet the ICH standards, as outlined in Q3B and should not be allowed to double the qualified threshold.**

3. The draft guidance also allows qualification of new or higher level degradation products via structure-toxicology analysis (QSAR). This provision is not allowed for NDAs nor is it part of ICH Q3B. **QSAR should not be used in qualifying new or higher levels of degradation products in ANDAs.**

4. The basis for qualification of impurities for new products (i.e. NDAs) is genetic toxicology and whole animal toxicology testing according to ICH Q3B. The proposed ANDA guidance requires only QSAR analysis or genetic toxicology, which is inadequate to assess the toxicology of new degradation products according to current FDA practice and ICH Q3B. Since additional (whole animal or in vivo) toxicology studies cannot be used for generic drug products, an NDA would be required. **Therefore, in situations where new degradation products appear, we believe the product is substantially different from the innovator, and that an ANDA cannot be used to gain approval.**

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[1] 21 C.F.R. 314.430(g)(1) exempts disclosure of methods for manufacturing processes, including quality control procedures. We acknowledge; however, that 21 C.F.R. 314.430(e)(6) allows disclosure of analytical methods unless: (1) Extraordinary circumstances, (2) Method serves no regulatory or compliance purpose, and (3) the method falls within the exemption for trade secrets and confidential commercial information. Putting the two regulations together, it seems clear that analytical methods (like degradation assays) cannot be disclosed if they constitute manufacturing procedures, including quality control procedures.

ATTACHMENT

FDA's December 1998 Draft Guidance for Industry— ANDAs: Impurities in Drug Products -- FOIA Concerns

The Food and Drug Administration's ("FDA") December 1998 Guidance for Industry "ANDAs: Impurities in Drug Products," includes a provision in Part 2 of Section VII. (Qualifying Impurities, Comparative Chromatographic Studies), that states, "... analytical procedures for the [referenced listed drug] may be requested from the Agency under the Freedom of Information Act (FOIA)."[1] It is our position that providing such information under FOIA would violate the public information provisions of the Administrative Procedure Act ("APA")[2] (known as the Freedom of Information Act or "FOIA") as well as FDA's regulations.[3]

I. Disclosure Prohibitions in FDA's Regulations

With regard to the public disclosure of data and information in a new drug application ("NDA"), FDA's regulations state, "Manufacturing methods or processes, including quality control procedures," are not available for public disclosure unless they have been previously disclosed to the public or relate to a product or ingredient that has been abandoned, and they do not represent a trade secret or confidential commercial information.[4] The specifications in the

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[1]FDA, Draft Guidance for Industry: ANDAs: Impurities in Drug Products (December 1998). Congress has made clear both that the federal courts, and not the administrative agencies, are ultimately responsible for construing the language of the FOIA, and that agencies cannot alter the dictates of the Act. Public Citizen Health Research Group v. Food and Drug Administration, 704 F.2d 1280, 1287 (D.C. Cir. 1983).

[2]5 U.S.C. § 552.

[3]21 C.F.R. § 20.

[4]21 C.F.R. § 314.430(g)(1). FDA's regulations at 21 C.F.R. § 314.430(e)(6) state that an assay method or other analytical method is available for disclosure unless: (1) there

approved NDA for a drug product are the quality controls which ensure the consistent quality and purity of that product. As defined in the glossary of the Draft Guidance, specifications are "a list of tests, reference to analytical procedures and appropriate criteria which are numerical limits, ranges, or other criteria for the tests described." Thus, the analytical procedure for determining the presence of impurities/degradation products is included in the specifications used to control the quality and purity of the product, and it is, by definition, a quality control procedure. Since the analytical procedures used by an innovator company to detect and quantify degradation products in RLDs are quality control procedures, they are, therefore, inappropriate for disclosure.

In addition, the analytical procedures used by an innovator company to detect and quantify degradation products in referenced listed drugs ("RLD") are confidential "trade secrets" and/or "commercial information" under the APA,[5] and, thus, are inappropriate for release under FOIA. FDA's regulations state that trade secrets and commercial information are not available for public disclosure.[6]

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are extraordinary circumstances; (2) the method serves no regulatory or compliance purpose; and (3) the method falls within the exemption for trade secrets and confidential commercial information. As FDA has promulgated both of these regulations, the Agency must have intended that they not conflict. The logical interpretation of how these regulations are to work together is that assay or analytical methods information can be disclosed unless these methods constitute manufacturing methods or procedures, including quality control procedures. Otherwise, analytical procedures that are quality control procedures would be disclosable, which would be in direct violation of 21 C.F.R. § 314.430(g)(1).

[5] 5 U.S.C. § 552(b)(4). The FOIA exemption for trade secrets and confidential commercial information could cover such materials as "scientific or manufacturing processes or developments." H.R. REP. NO. 1497, 89th Cong., 2d Sess. 10 (1966).

[6] 21 C.F.R. § 20.61. Also see 21 C.F.R. § 20.21; 21 C.F.R. § 314.430(e)(3) (a protocol for a test or study, contained in an NDA, ANDA, SNDA, IND, or drug master file, cannot be disclosed if it is a trade secret or confidential commercial information).

II. Prohibitions on Disclosure of Trade Secrets

FDA's regulations state that a trade secret "may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort."[7] In addition, "[t]here must be a direct relationship between the trade secret and the productive process."[8]

The full reports of safety and effectiveness data submitted as part of an NDA have been determined to be trade secrets,[9] and FDA has freely admitted that drug manufacturers maintain a property interest in the sensitive information which is supplied to the Agency.[10] The analytical procedures used by an innovator company to detect and quantify degradation products in RLDs are part of the specifications and analytical methods that are necessary to assure the quality and purity of a drug substance, as required in the "chemistry, manufacturing, and controls section" of an NDA.[11]

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[7]21 C.F.R. § 20.61. Also see Public Citizen Health Research Group, 704 F.2d at 1288.

[8]Id.

[9]Anderson v. Department of Health and Human Services, 907 F.2d 936 (10th Cir. 1990) (documents under the descriptive category of "manufacturing and processing information, including formulations, chemistry and quality assurance procedures" are within the definition of trade secrets; the majority of information in an IND, NDA, and IDE are likely trade secrets). Also see Syntex Corp., et. al., v. Joseph A. Califano, Jr., 1978-80 FDLI Jud. Rec. 970 (D.D.C. 1979).

[10]39 Fed. Reg. 44612.

[11]21 C.F.R. § 314.50(d)(1)(I). Manufacturers may reveal portions of their NDAs to outside consultants or governmental employees on a need-to-know basis, to the extent necessary to gain approval from the FDA, without destroying the confidentiality of this information. 21 C.F.R. § 20.81(a)(1), (3).

The analytical procedures used by an innovator company to detect and quantify degradation products in RLDs are, by definition, processes used to prepare drugs, and are the product of substantial effort. Drug preparation and processing are complex and diverse activities, and must address the unique characteristics of a drug's active ingredients, excipients, and other inactive ingredients. The processes used to detect and quantify degradation products are tailored to the unique chemical and production characteristics of each drug, and are therefore directly related to the productive process of a given drug. In addition, these processes are commercially valuable in that they directly impact the quality of a sponsoring company's drug, and can provide information that would benefit other companies and justify commercial investment. Therefore, the analytical procedures used by an innovator company to detect and quantify degradation products in RLDs are trade secrets under FDA's regulations, and exempt from disclosure under FOIA.

III. Prohibitions on Disclosure of Commercial Information

FDA's FOIA regulations state that commercial information that is privileged or confidential means, "valuable data or information which is used in one's business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs."[12] Commercial matter is confidential if the information will "cause substantial harm to the competitive position of the person from whom the information was obtained",[13] which in the context of FOIA, is to be determined on the basis of whether there is "actual competition and the likelihood of substantial competitive injury."[14]

Drug manufacturers have a commercial interest in health and safety information concerning their products,[15] and safety and effectiveness information about a manufacturer's drug may be

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[12] 21 C.F.R. § 20.61(b).

[13] National Ass'n of Gov't Employees v. Campbell, 593 F.2d 1023, 1026 (D.C. Cir. 1978).

[14] Gulf & Western Industries, Inc. v. United States, 615 F.2d 527, 530 (D.C. Cir. 1979). Barring extraordinary circumstances, all safety and effectiveness data submitted in an application can be disclosed to the public if no work is being or will be undertaken to have the application approved, a final determination has been made that the application is not approvable and all legal appeals have been exhausted, approval of the application is withdrawn and all legal appeals have been exhausted, and a final determination has been made that the new drug is not a new drug. 21 C.F.R. § 314.430(f). Also see Public Citizen Health Research v. Food and Drug Administration, 997 F. Supp. 56, 70 (D.D.C. 1998) (at the time that no work is or will be done on an IND application, safety and effectiveness data is to be released, barring extraordinary circumstances).

[15] Public Citizen Health Research Group, 704 F.2d at 1290 (because documentation of the health and safety experience of drug/device products is instrumental in gaining marketing approval for such products, manufacturers have a commercial interest in such health and safety information). Study protocols are not disclosable if they fall within the exemption for trade secrets and confidential commercial information. 21 C.F.R. § 314.430(e)(3).

of great assistance to competing drug manufacturers, and therefore a potential cause of "substantial commercial injury.[16] "A drug manufacturer that has submitted an NDA has a competitive interest in seeing that the information in its NDA is not prematurely released to the public. If a manufacturer's competitor could obtain all the data in the manufacturer's NDA, it could utilize them in its own NDA without incurring the time, labor, risk, and expense involved in developing them independently."[17] Therefore, the release of the types of data and information in NDA and IND files have been previously held to constitute "substantial commercial harm" in relation to the FOIA exemption for commercial information.[18]

As an example of the type and magnitude of commercial injury an innovator drug company would face if the analytical procedures developed to detect and quantify degradation products were disclosed, consider the following. Given that the development of the analytical procedure itself typically requires six months calendar time and costs in the range of $150,000 - $300,000, the immediate and most obvious commercial injury would be $150 - 300,000 which the competitor would not have to put at risk to bring the generic product to market. Even more significant, however, would be the loss in sales suffered by the innovator since disclosure would allow the competitor to use the information to market the competing product six months earlier. It has been demonstrated in numerous instances that sales of an innovator's product will suffer a decline of at least 20-30% in the first six months of generic competition. Even for a product with relatively modest annual sales of $240 million, the loss to the innovator due to disclosure of the analytical procedure would be about $30 million.

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[16]Public Citizen Health Research Group, 997 F. Supp. at 62.

[17]Webb v. Dept. of Health and Human Services, 696 F.2d 101, 103 (D.C. Cir. 1982).

[18]Public Citizen Health Research Group, 997 F. Supp. at 62.

Further, the analytical methods used to quantify impurities in the drug product are generally the same as those used to detect and minimize impurities in the drug substance, where the removal of impurities is important for safety reasons. If methods used to quantify impurities for the drug product are disclosable, a generic competitor could then easily determine the proprietary procedures used for the drug substance, procedures which are also protected under FOIA.[19] Perhaps even more detrimental, disclosure of the drug substance procedures would enable the competitor to analyze the manufacturing methods for the drug substance -- which are explicitly prohibited from FOIA disclosure pursuant to 21 C.F.R. § 314.430(g)(1). Providing an avenue for disclosure of protected manufacturing information would obviously provide a significant commercial benefit to a potential competitor, and represent a substantial commercial injury to a manufacturer.

Accordingly, the analytical procedures used by an innovator company to detect and quantify degradation products is "valuable data or information," and the release of this information would provide a competitor with a commercial advantage. Innovator drug companies face enormous competition, both within therapeutic drug class by manufacturers with competing medications, as well as by generic drug companies and their offerings. If competing companies can obtain information concerning the proprietary processing standards employed by an innovator drug company, competing innovator and generic drug manufacturers could use this information to learn more about the underlying properties of a company's drug, and potentially adopt useful processing techniques to improve their own drug products. An innovator drug company would be substantially injured by any decrease in its competitive advantage in such a fiercely competitive industry. Therefore, the analytical procedures used

[19]Unlike the December 1998 Draft Guidance, FDA's Draft Guidance for Industry, ANDAs: Impurities in Drug Substances (June 1998) does not state that analytical procedures are available through FOIA.

by an innovator company to detect and quantify degradation products constitute confidential information under FOIA, and cannot be disclosed.

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